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ORIGINAL ARTICLE

Assessment of diastolic reserve in hypertensive patients by dobutamine stress Doppler tissue imaging

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KEYWORDS

Hypertension;
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Abstract *Background:* Many hypertensive patients are symptomatic mainly with exercise, because of the rise in filling pressures. Therefore, it is useful to evaluate left ventricular filling pressure with exercise. The study aims to determine the role of dobutamine stress echocardiography in assessment of diastolic reserve in hypertensive patients with normal ejection fraction.
Methods and results: 30 Hypertensive patients (53.8 ± 4.1 years) and 20 sex and age-matched healthy controls (51.9 ± 9.7 years) were recruited. Patients with coronary artery disease, significant valvular disease, hypertrophic cardiomyopathy, left ventricular systolic dysfunction (EF < 50%), atrial fibrillation and bad echogenic view were excluded. All groups underwent complete conventional echo and dobutamine stress echocardiography using pulsed wave Doppler tissue imaging at rest and during peak stress to measure early mitral inflow diastolic wave velocity (E), late mitral inflow diastolic wave velocity (A), E/A ratio, early diastolic myocardial wave velocity (E') and late diastolic myocardial wave velocity (A'). At rest; E' was significantly lower in patients than controls (9.3 ± 1.8 vs 14.9 ± 2.4 P value < 0.001) and E/E' (early mitral inflow diastolic wave velocity/early myocardial diastolic wave velocity) was significantly higher in patients (7.7 ± 1.3 vs 5.1 ± 1.0 P

Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; DTI, Doppler tissue imaging; DSE, dobutamine stress echocardiography; LV, left ventricular; EF, ejection fraction; E, early mitral inflow diastolic wave velocity; A, late mitral inflow diastolic wave velocity; S', systolic wave velocity; E', early diastolic wave velocity; A', late diastolic wave velocity; ICT, isometric contraction time; IRT, isometric relaxation time; E/E' ratio, early mitral inflow diastolic wave velocity/early myocardial diastolic wave velocity; LVDP, left ventricular diastolic pressure.

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value <0.001). At peak stress; E/A ratio was significantly lower in patients ($P < 0.001$) while E/E' was significantly higher in patients than controls (8.4 ± 2.2 vs 4.8 ± 0.8 P value <0.001).
Conclusions: Dobutamine stress echocardiography using Doppler tissue imaging is useful in hypertensive patients with exertional dyspnea with normal resting filling pressure.

1. Introduction

Hypertension is the most common, readily, identifiable, and reversible risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection, and peripheral arterial disease.[2] Impaired left ventricular diastolic filling is also a common finding in hypertensive patients, especially in those with ventricular hypertrophy, even in the absence of evidence of decreased systolic performance.[3]

In many patients with essential hypertension in the absence of coronary artery disease, left ventricular systolic and diastolic function is normal at rest but may respond abnormally during exercise and develop exertional dyspnea even with good systolic function during exercise.[3] This phenomenon may reflect impaired left ventricular diastolic filling at stress and this is called lack of diastolic reserve[4]

Impaired diastolic reserve is defined as: (A) under baseline condition: no or mild degree of diastolic dysfunction and normal filling pressures. (B) Under stress or during exercise: overt diastolic dysfunction with elevated filling pressure and complaints of dyspnea.[4]

The E/E' ratio has been applied for that objective. In subjects with normal myocardial relaxation, E and E' velocities increase proportionally, and the E/E' ratio remains unchanged or is reduced.[5] However, in patients with impaired myocardial relaxation, the increase in E' with exercise is much less than that of mitral E velocity, such that the E/E' ratio increases.[6] In that regard, E/E' was shown to relate significantly to LV filling pressures during exercise, when Doppler echocardiography was acquired simultaneously with cardiac catheterization.[1]

Dobutamine stress echocardiography (DSE) is an accurate and noninvasive technique that is widely used for the detection of underlying coronary artery disease (CAD).[7] Using Doppler tissue imaging (DTI), a dobutamine-induced reduction in the peak annular velocities in systole and diastole has been demonstrated to identify CAD.[8]

It is most useful in hypertensive patients with unexplained exertional dyspnea who have mild diastolic dysfunction and normal filling pressures at rest. In those patients the E/E' ratio increases with exercise.[6]

2. Patients and methods

2.1. Patient selection

Thirty hypertensive patients (11) males and (19) females with mean age (53.8 ± 4.1) years were enrolled who were referred to the cardiology clinic in the Menoufyia University and (20) age and sex matched, apparent healthy, individuals as the control group. All participants provided informed consent and the study protocol was approved by the institutional ethics committee.

Hypertension was defined as a previous blood pressure recording on 2 separate occasions of >140 mmHg systolic or >90 mmHg diastolic or the ongoing prescription of antihypertensive medication.[9]

Patients with CAD, significant valvular disease, hypertrophic cardiomyopathy, left ventricular systolic dysfunction (EF $<50\%$), AF and bad echogenic view were excluded.

Patients underwent detailed history, thorough clinical examination, 12 lead ECG, and complete echocardiogram.

2.2. Conventional echocardiography

Echocardiographic examination was done by using the commercially available (Vivid 9, General Electronic Healthcare, GE Vingmed, Norway) equipped with a 1.7–4 MHz phased-array transducer. Echocardiographic imaging was obtained in the parasternal long- and short-axis, and apical two, three and four-chamber views using standard transducer positions (LV end-diastolic and end-systolic diameters, septal and posterior wall thickness and ejection fraction) were measured in accordance with the recommendations of the American Society of Echocardiography.[10]

From the apical window, a 1- to 2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from 5 to 10 cardiac cycles were recorded. The mitral inflow velocities were traced and the following variables were obtained: peak velocity of early diastolic wave velocity (E), late diastolic wave velocity (A) and E/A ratio.[11] (Fig. 1).

Doppler tissue imaging of the mitral annulus was obtained from the apical 4-chamber view. A 1.5-mm sample volume was placed at the lateral annulus. Analysis was performed for the measurement of systolic wave velocity (S'), early diastolic wave velocity (E'), late diastolic wave velocity (A'), E'/A' ratio, isometric relaxation time (IRT) and isometric contraction time (ICT) at rest. E/E' ratio at rest was calculated.[12]

2.3. Dobutamine stress protocol[13]

Beta-adrenergic blocking agents were withdrawn for the preceding 48 h prior to the study. Dobutamine was infused at doses of 5, 10, 20, 30 and 40 μg/kg/min for 3 min each. A 12-lead electrocardiogram, blood pressure, and two-dimensional (2D) echocardiograms were taken at baseline, at low dose dobutamine, peak dobutamine, and at recovery (Fig. 2).

Transmitral flow was used to measure (early diastolic wave velocity (E), late diastolic wave velocity (A) and E/A ratio) at peak dose using DTI lateral mitral annular velocities; systolic wave velocity (S'), early diastolic wave velocity (E'), late diastolic wave velocity (A'), E'/A' ratio, isometric relaxation time (IRT) and isometric contraction time (ICT) were measured at peak dose (Fig. 3). E/E' ratio at peak stress was calculated.[12]

The stress test was terminated when 85% of the maximal predicted heart rate was reached, or earlier if the patient had

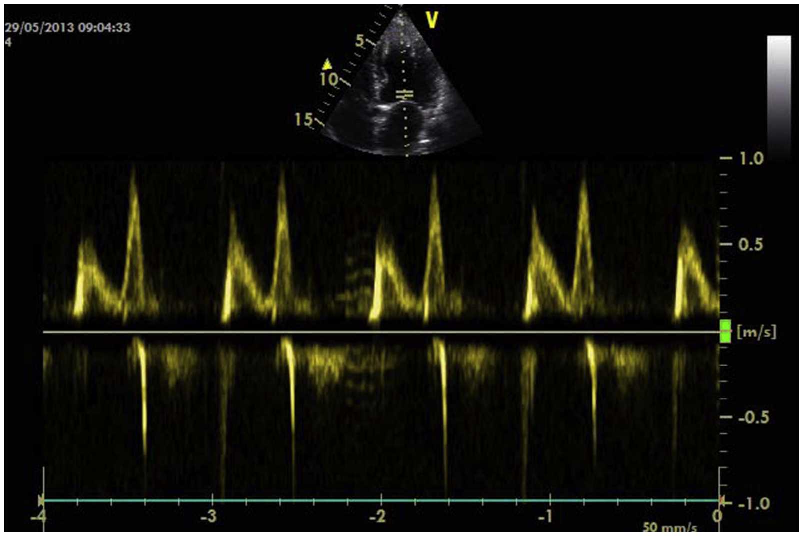

Figure 1 Pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities were obtained: peak velocity of early diastolic wave velocity (E), late diastolic wave velocity (A) and E/A ratio.

progressive or severe chest discomfort, serious ventricular arrhythmia, systolic blood pressure >240 mmHg, symptomatic hypotension or systolic blood pressure <80 mmHg or intolerable side effects.[13]

2.3.1. Statistical analysis

Using statistical package for the social science software (SPSS) version 16, data from the patients and controls were collected and subjected to statistical analysis.

The level of significance is 95%. So, P value >0.05 was considered a non significant result, that <0.05 was considered a significant result, and that <0.001 was considered a highly significant result.

3. Results

Hypertensive patients have significantly lower E' and E'/A' than controls while E/E' ratio was significantly higher in hypertensive patients than controls. Similarly isometric relaxation time (IRT) was significantly prolonged in hypertensive patients than controls (Tables 1–3).

Hypertensive patients have significantly higher A (late mitral inflow diastolic wave velocity) and significantly lower E/A ratio at peak stress than control.

By DTI hypertensive patients have significantly lower E' and A' at peak stress than control. On the other hand both E'/A' ratio and E/E' ratio were significantly higher in patients than control. Isometric relaxation time (IRT) was significantly prolonged in patients than controls (Table 4).

All conventional echo measurements were significantly higher at peak stress than at rest in hypertensive patients (P value <0.001).

By DTI there was a highly significant increase in systolic wave velocity (S') [P value <0.001] and a significant increase in late diastolic wave velocity (A') [P value <0.05] at peak stress than at rest in hypertensive patients. Both isometric contraction time (ICT) and isometric relaxation time (IRT) were significantly shortened at peak stress than at rest in hypertensive patients (P value <0.001).

E/E' was higher at peak stress than at rest in hypertensive patients but did not reach a significant value (P value >0.05).

By conventional echo; ejection fraction, E (early mitral inflow diastolic wave velocity) and A (late mitral inflow diastolic wave velocity) were significantly higher at peak stress than at rest in studied controls (P value <0.001) as demonstrated in Table 5.

The comparison between resting and stress echo measurements in the studied controls by DTI revealed that there was a highly significant increase in systolic wave velocity (S') and late diastolic wave velocity (A') [P value <0.001] at peak stress than at rest. Similarly there was a significant increase in early diastolic wave velocity (E') [P value <0.05] at peak stress. Isometric contraction time (ICT) was significantly shortened at peak stress (P value <0.001).

E/E' was lower at peak stress than at rest in studied controls but did not reach a significant value (P value >0.05).

4. Discussion

Chronic hypertension is the most common cause of diastolic dysfunction and failure. It leads to left ventricular hypertrophy and increased connective tissue content, both of which decrease cardiac compliance.[14] The hypertrophied ventricle has a steeper diastolic pressure–volume relationship; therefore, a small increase in left ventricular end-diastolic volume (which can occur with exercise) causes a marked increase in left ventricular end diastolic pressure.[14]

An increase in left ventricular diastolic pressure (LVDP) is an important cardiac cause of exertional dyspnea.[15] These symptoms often occur in patients with early myocardial abnormalities such as those seen in hypertensive and diabetic heart disease[16,17] and are independent of the influence of exercise-induced ischemia. Ejection fraction is characteristically preserved in these patients, but although such patients may be labeled as having diastolic heart failure,[18–21] resting diastolic filling patterns may be normal, even in the presence of demonstrable myocardial structural abnormalities.[22]

Previous work has shown that, under resting conditions, LVDP can be estimated noninvasively by Doppler techniques.[23]

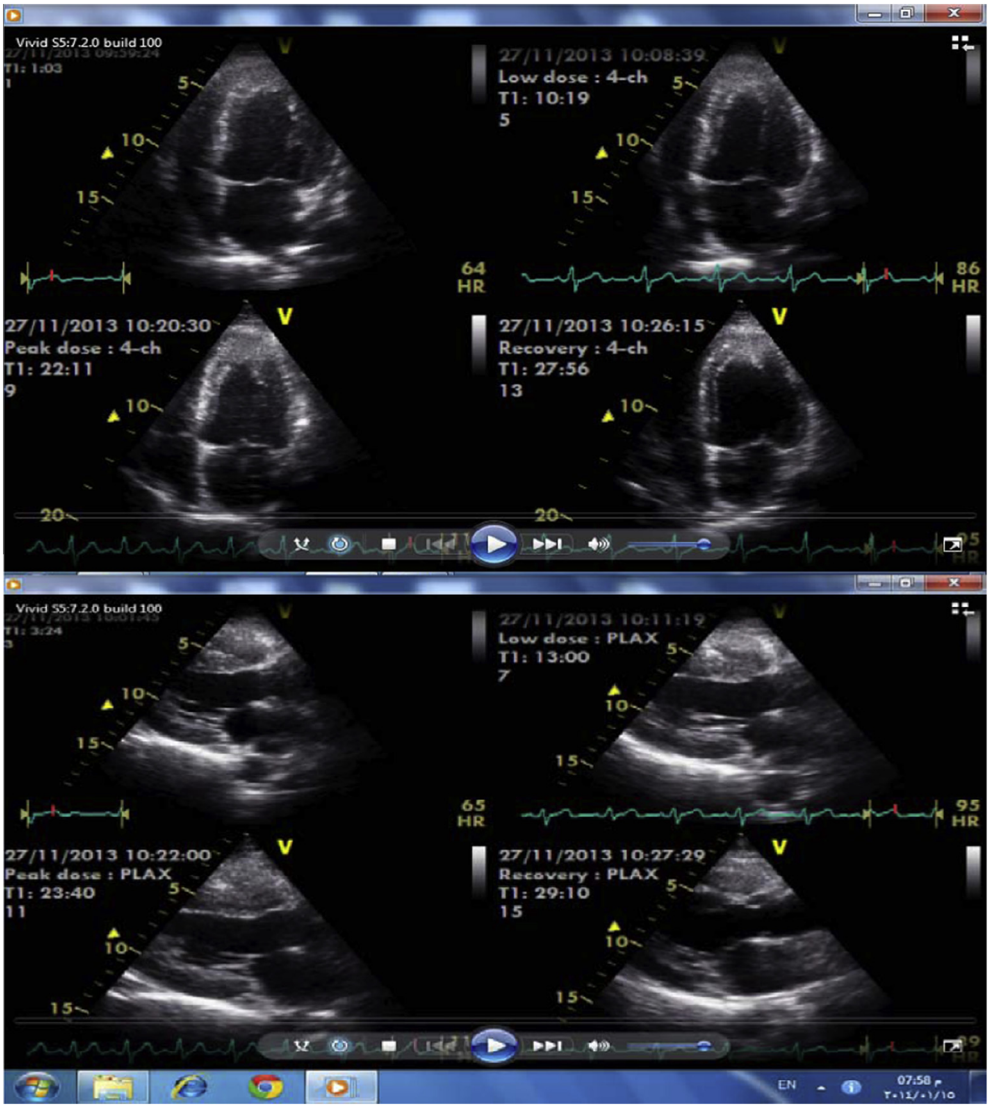

Figure 2 Quad view during dobutamine stress echo in hypertensive patient; the upper panel in apical four chamber view and the lower one in parasternal long axis view.

The ratio of early diastolic transmitral velocity to tissue velocity (E/E') correlates with LVDP, and an E/E' of >15 has been found to be a reliable means of predicting an elevated LVDP.[24] Measurement of E/E' during physical exercise may give a more clinically relevant assessment of the effects of changes in LVDP on exercise capacity.[1]

In this study we assessed the diastolic function of the heart in two groups that have preserved EF (30 hypertensive patients and 20 control group) using conventional Echocardiography and DTI during rest and during peak stress using dobutamine stress echocardiography and we studied the abnormalities in diastolic function and diastolic reserve in hypertensive patients.

We used DTI to measure mitral annulus velocities at lateral wall because a number of recent studies have noted that in patients with normal EF, lateral tissue Doppler signals (E/E' and E'/A') have the best correlations with LV filling pressures and invasive indices of LV stiffness. These studies favored the use of lateral tissue Doppler signals in this population.[25]

At rest; the present study showed no significant difference at early diastolic wave velocity (E), late diastolic wave velocity (A) and E/A ratio between hypertensive patients and the control group, this agreed with Verdecchia et al. who found no significant difference in E, A and E/A ratio between hypertensive patients and control.[26]

Resting DTI revealed no significant difference between hypertensive patients and controls in systolic wave velocity (S'), and isometric contraction time (ICT); this finding was similar to Bruch et al.[27] who found no significant difference in S' between two groups. While isometric relaxation time (IRT) was significantly prolonged in patients than controls (P value <0.001) this agreed with Sevleta et al. who found that isometric relaxation time (IRT) is longer in patients with diastolic dysfunction.[28]

In agreement with our result; Steen et al. found that there was no significant difference in late diastolic velocity of the mitral annulus (A') between hypertensive and control.[29]

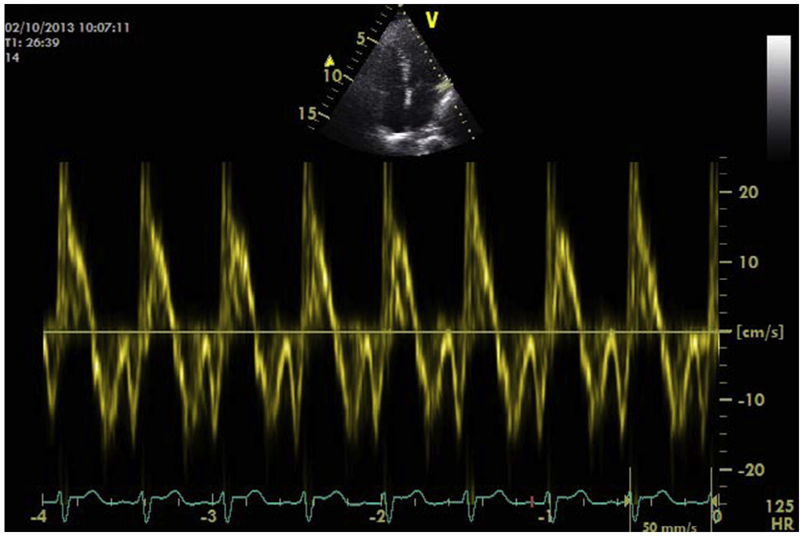

Figure 3 Pulsed wave Doppler tissue imaging at lateral mitral annulus at peak stress showing systolic velocity (S'), early diastolic velocity (E') and late diastolic velocity (A').

Table 1 Demographic data of both groups.

	Patients No. = 30	Controls No. = 20	Test of significance	P value
Age	53.8 ± 4.1	51.9 ± 9.7	t-test 0.83	0.42
	No	No	χ^2	
Sex			0.88	0.35
Male	11 (36.7%)	8 (40%)		
Female	19 (63.3%)	12 (60%)		

Table 2 Echocardiographic measurements in studied groups at rest.

	Patients No. = 30	Controls No. = 20	Test of significance t-test	P value
EF%	61.5 ± 3.6	62.6 ± 3.2	1.12	0.26
E	70.5 ± 10.5	73.5 ± 3.4	1.46	0.15
A	75.2 ± 11.5	73.4 ± 7.3	0.61	0.55
E/A	0.95 ± 0.16	1.02 ± 0.15	1.42	0.16
S'	8.4 ± 0.9	8.9 ± 1.2	1.68	0.09
E'	9.3 ± 1.8	14.9 ± 2.4	9.34	< 0.001
A'	9.9 ± 2.2	11.0 ± 3.3	1.28	0.21
E'/A'	0.98 ± 0.27	1.47 ± 0.51	4.04	< 0.001
ICT	70.5 ± 13.5	66.2 ± 4.3	1.61	0.12
IRT	79.6 ± 15.8	48.7 ± 9.6	7.79	< 0.001
E/E'	7.7 ± 1.3	5.1 ± 1.0	7.50	< 0.001

EF: ejection fraction, E: early mitral inflow diastolic wave velocity, A: late mitral inflow diastolic wave velocity, S': systolic wave velocity, E': early diastolic wave velocity, A': late diastolic wave velocity, ICT: isometric contraction time, IRT: isometric relaxation time.

On the contrary our study found that E' was significantly lower in hypertensive patients than controls; this went in harmony with Ommen et al. who concluded that the early diastolic velocity (E') is reduced in patients with conditions leading to an impaired relaxation such as LVH or restrictive cardiomyopathy, where E decreases as LV filling pressure increases.[24]

Resting E/E' ratio was significantly higher in hypertensive patients than controls. Nagueh et al. concluded that E/E' is helpful as a tool for assessing LV filling pressures that combines the influence of transmitral driving pressure and myocardial relaxation and it is identified as the best parameter for diagnosis when compared to other Doppler measures.[23–30]

Ommen et al. found that E/E' ratio had a better correlation with invasively measured LVDP than did other Doppler variables for all levels of diastolic function and concluded that the E/E' ratio be used as the initial measurement for estimation of LV filling pressures, particularly in those patients with preserved systolic function.[24]

Analysis of systolic function at peak stress revealed a significant increase in EF% and S' compared to rest in both

Table 3 Comparison between echocardiographic measurements in studied groups at peak stress.

	Patients No. = 30	Controls No. = 20	Test of significance *t*-test	*P* value
EF%	70.4 ± 2.8	71.1 ± 2.4	0.96	0.34
E	77.9 ± 16.5	81.4 ± 9.9	0.84	0.41
A	98.4 ± 13.4	87.4 ± 12.6	2.93	0.005
E/*A*	0.79 ± 0.10	0.95 ± 0.18	3.61	0.001
S′	13.0 ± 2.1	13.9 ± 1.7	1.60	0.12
E′	9.7 ± 2.4	17.5 ± 3.5	8.64	< 0.001
A′	11.2 ± 1.7	14.3 ± 3.5	3.76	0.001
E′/*A*′	0.89 ± 0.27	1.29 ± 0.37	4.48	< 0.001
ICT	52.1 ± 8.5	48.2 ± 7.4	1.70	0.09
IRT	61.3 ± 17.4	46.6 ± 5.0	4.38	< 0.001
E/*E*′	8.4 ± 2.2	4.8 ± 0.8	8.22	< 0.001

EF: ejection fraction, *E*: early mitral inflow diastolic wave velocity, *A*: late mitral inflow diastolic wave velocity, *S*′: systolic wave velocity, *E*′: early diastolic wave velocity, *A*′: late diastolic wave velocity, ICT: isometric contraction time, IRT: isometric relaxation time.

Table 4 Comparison between resting and stress echo measurements in the studied patients.

	Resting	Peak stress	Test of significance *t*-test	*P* value
EF%	61.5 ± 3.6	70.4 ± 2.8	26.77	< 0.001
E	70.5 ± 10.5	77.9 ± 16.5	2.37	0.02
A	75.2 ± 11.5	98.4 ± 13.4	9.91	< 0.001
E/*A*	0.95 ± 0.16	0.79 ± 0.10	4.29	< 0.001
S′	8.4 ± 0.9	13.0 ± 2.1	12.43	< 0.001
E′	9.3 ± 1.8	9.7 ± 2.4	0.83	0.41
A′	9.9 ± 2.2	11.2 ± 1.7	3.36	0.002
E′/*A*′	0.98 ± 0.27	0.89 ± 0.27	1.56	0.13
ICT	70.5 ± 13.5	52.1 ± 8.5	8.05	< 0.001
IRT	79.6 ± 15.8	61.3 ± 17.4	8.25	< 0.001
E/*E*′	7.7 ± 1.3	8.4 ± 2.2	1.47	0.15

EF: ejection fraction, *E*: early mitral inflow diastolic wave velocity, *A*: late mitral inflow diastolic wave velocity, *S*′: systolic wave velocity, *E*′: early diastolic wave velocity, *A*′: late diastolic wave velocity, ICT: isometric contraction time, IRT: isometric relaxation time.

Table 5 Comparison between resting and stress echo measurements in the studied control.

	Resting	Peak stress	Test of significance t-test	P value
EF%	62.6 ± 3.2	71.1 ± 2.4	24.95	< 0.001
E	73.5 ± 3.4	81.4 ± 9.9	3.32	0.004
A	73.4 ± 7.3	87.4 ± 12.6	5.52	< 0.001
E/*A*	1.02 ± 0.15	0.95 ± 0.18	1.41	0.17
S′	8.9 ± 1.2	13.9 ± 1.7	24.37	< 0.001
E′	14.9 ± 2.4	17.5 ± 3.5	2.87	0.01
A′	11.0 ± 3.3	14.3 ± 3.5	4.08	< 0.001
E′/*A*′	1.47 ± 0.51	1.29 ± 0.37	1.75	0.09
ICT	66.2 ± 4.3	48.2 ± 7.4	13.01	< 0.001
IRT	48.7 ± 9.6	46.6 ± 5.0	0.73	0.48
E/*E*′	5.1 ± 1.0	4.8 ± 0.8	0.99	0.33

EF: ejection fraction, *E*: early mitral inflow diastolic wave velocity, *A*: late mitral inflow diastolic wave velocity, *S*′: systolic wave velocity, *E*′: early diastolic wave velocity, *A*′: late diastolic wave velocity, ICT: isometric contraction time, IRT: isometric relaxation time.

hypertensive and control groups while there was no significant difference in ejection fraction between patients and controls at peak stress, this agreed with Ha et al.[6]

Regarding diastolic function; there was a significant decrease in *E*/*A* ratio at peak stress in patients than controls; this was similar to Hildo et al. who revealed that *E*/*A* ratio decreased at peak stress in hypertensive than controls.[31]

In our study *E*/*E*′ ratio showed a significant increase in the hypertensive group at peak stress than at rest this can be explained as subjects with normal myocardial relaxation, *E* and *E*′ velocities increase proportionally, and the *E*/*E*′ ratio remains unchanged or is reduced.[5] However, in patients with impaired myocardial relaxation, the increase in *E*′ with exercise is much less than that of mitral *E* velocity so that the *E*/*E*′ ratio increases.[6] In that regard, *E*/*E*′ was shown to relate significantly to LV filling pressures during exercise, when Doppler echocardiography was acquired simultaneously with cardiac catheterization.[1]

Malcolm et al. concluded that the E/E' correlates with invasively measured LVDP during exercise. It can be used to reliably identify patients with elevated LVDP during exercise and reduced exercise capacity.[1] This increase in filling pressure is a recognized phenomenon in a significant proportion of patients complaining of dyspnea and supports a cardiac cause of dyspnea.[32]

5. Conclusion

Dobutamine stress Doppler tissue imaging is most useful in hypertensive patients with preserved left ventricular systolic function presented by unexplained exertional dyspnea and diastolic dysfunction. It can detect the diminished diastolic reserve in these hypertensive patients by increased E/E' ratio at stress which is a parameter of LV filling pressure.

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Conflict of interest

No conflict of interests for all the authors for any financial support related to this study.

References

1. Malcolm I, Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;**47**:1891–900.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;**289**(19): 2560–72.
3. Slama M, Susic D, Varagic J, Frohlich ED. Diastolic dysfunction in hypertension. *Curr Opin Cardiol* 2002;**17**:368–73.
4. Thierry Gillebert (Gent, BE) the concept of diastolic reserve. 2010 ESC Congress 28 Aug 2010–01 Sep 2010, Stockholm, Sweden.
5. Ha JW, Lulic F, Bailey KR, Pellikka PA, Seward JB, Tajik AJ, et al. Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. *Am J Cardiol* 2003;**91**:114–5.
6. Ha JW, Oh JK, Pellikka PA, Ommen SR, Stussy VL, Bailey KR, et al. Diastolic stress echocardiography: a novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. *J Am Soc Echocardiogr* 2005;**18**:63–8.
7. Wake R, Takeuchi M, Yoshitani H, Miyazaki C, Otani S, Yoshiyama M, et al. Role of contrast-enhanced dobutamine stress echocardiography in predicting outcome in patients with known or suspected coronary artery disease. *Echocardiography* 2006;**23**: 642–9.
8. von Bibra H, Tuchnitz A, Klein A, Schneider EJ, Schömig A, Schwaiger M. Regional diastolic function by pulsed Doppler myocardial mapping for the detection of left ventricular ischemia during pharmacological stress testing. *J Am Coll Cardiol* 2000;**36**: 444–52.
9. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. *Circulation* 2012;**125**(1):e2–e220.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Members of the chamber quantification writing group: recommendations for chamber quantification: a report from the American society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–63.
11. Ommen SR, Nishimura RA. A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography. *BMJ* 2003;**89**:9–18.
12. Chattopadhyay S, Alamgir MF, Nikitin NP, Rigby AS, Clark AL, Cleland JG. Lack of diastolic reserve in patients with heart failure and normal ejection fraction. *Circ Heart Fail* 2010;**3**:35–43.
13. Becher H, Chambers J, Fox K, Jones R, Leech GJ, Masani N, et al. BSE procedure guidelines for the clinical application of stress echocardiography, recommendations for performance and interpretation of stress echocardiography: a report of the British society of echocardiography policy committee. *Heart* 2004;**90**(Suppl. 6):vi23–30.
14. Lorell BH, Carabello BA. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation* 2000;**102**:470–9.
15. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;**17**:1065–72.
16. Maurer MS, Spevack D. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? *J Am Coll Cardiol* 2004;**44**:1543–9.
17. Klapholz M, Maurer M, Lowe AM, Messineo F, Meisner JS, Mitchell J, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York heart failure registry. *J Am Coll Cardiol* 2004;**43**: 1432–8.
18. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;**350**:1953–9.
19. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part I: diagnosis, prognosis and measurements of diastolic function. *Circulation* 2002;**105**:1387–93.
20. Burkhoff D, Maurer MS. Heart failure with a normal ejection fraction: is it really a disorder of diastolic function? *Circulation* 2003;**107**:656–8.
21. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiological perspective. *J Am Coll Cardiol* 1995;**26**:1565–74.
22. Walter JP, Dirk LB, Thierry CG, Frank ER, Stanislas U, Adelino FL, et al. European study group on diastolic heart failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;**19**:990–1003.
23. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;**30**:1527–33.
24. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures. A comparative simultaneous Doppler-catheterization study. *Circulation* 2000;**102**:1788–94.
25. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. *Circulation* 2007;**11**: 637–47.
26. Verdecchia P, Schillaci G, Guerrieri M, Boldrini F, Gatteschi C, Benemio G, et al. Prevalence and determinants of left ventricular diastolic filling abnormalities in an unselected hypertensive population. *Eur Heart J* 1990;**11**(8):679–91.

27. Bruch C, Marin D, Kuntz S, Schmermund A, Bartel T, Schaar J, et al. Analysis of mitral annulus excursion with tissue Doppler echocardiography. *Z Kardiol* 1999;**88**(5):353–62.
28. Avdić S, Mujcinović Z, Asćerić M, Nukić S, Kusljugić Z, Smajić E, et al. Left ventricular diastolic dysfunction in essential hypertension. *Bosn J Basic Med Sci* 2007;**7**(1):15–20.
29. Poulsen Steen H, Andersen Niels H, Ivarsen Per I, Mogensen Carl-Erik, Egeblad Henrik. Doppler tissue imaging reveals systolic dysfunction in patients with hypertension and apparent "isolated" diastolic dysfunction. *J Am Soc Echocardiogr* 2003;**16**:724–31.
30. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;**10**:165–9.
31. Lamb Hildo J, Beyerbacht Hugo P, van der Laarse Arnoud, Stoel Berend C, Doornbos Joost, van der Wall Ernst E, et al. Diastolic dysfunction in hypertensive heart disease is associated with altered myocardial metabolism. *Circulation* 1999;**99**:2261–7.
32. Talreja D, Nishimura R, Oh J. Non-invasive parameters of diastolic function reflect invasively measured filling pressures during exercise (abstr). *Circulation* 2004;**110**(Suppl.):III474.